The effects of manganese on glutamate, dopamine and -γ-aminobutyric acid regulation

By: Vanessa A. Fitsanakis, Catherine Au, Keith M. Erikson, and Michael Aschner

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Abstract:

Exposure to high levels of manganese (Mn) results in a neurological disorder, termed manganism, which shares a similar phenotype to Parkinson's disease due to the involvement of the basal ganglia circuitry in both. The initial symptoms of manganism are likely due to the involvement of the globus pallidus, a region rich in γ-aminobutyric acid (GABA) projections, while those of Parkinson's disease are related to the degeneration of the substantia nigra, a dopaminergic nucleus. Additionally, it is known that glutamate regulation is affected by increases in brain Mn levels. As Mn predominantly accumulates in the basal ganglia, it potentially could affect the regulation and interactions of all three neurotransmitters. This review will focus on the circuitry of these neurotransmitters within the basal ganglia and address potential sites for, as well as the temporal relationship, between Mn exposure and changes in the levels of these neurotransmitters. While most research has focused on perturbations in the dopaminergic system, there is evidence to support that early consequences of manganism also include disturbances in GABA regulation as well as glutamatergic-related excitotoxicity. Finally, we suggest that current research focus on the interdependence of these basal ganglial neurochemicals, with a greater emphasis on the GABAergic and glutamatergic systems.

Keywords: Manganese neurotoxicity; Glutamate; Dopamine; GABA; Basal ganglia

Article:

1. Introduction

Manganese (Mn) is a naturally occurring element present not only in the earth's crust, but also in many foods. Mn is an essential trace element, and under most conditions, humans consume sufficient amounts of Mn in their diet. However, occupations, such as Mn mining (Garcia-Avila and Penalver-Ballina, 1953; Rodier, 1955; Myers et al., 2003) and welding (Racette et al., 2001; Levy and Nassetta, 2003; Sadek et al., 2003) may present a greater risk for exposure, and by inference brain accumulation, of this metal. Under these circumstances, signs and symptoms characteristic of Mn toxicity have been recognized. Recent concern related to Mn exposure has also focused on the use of a Mn-containing fuel additive, methylcyclopentadienyl Mn tri-carbonyl (MMT), as an anti-knock agent in gasoline in Canada and other Western nations (Ressler et al., 1999; Bolte et al., 2004; Pfeifer et al., 2004; Rollin et al., 2005). Other data from animal studies suggest that iron deficiency or anemia may also be a risk factor for Mn neurotoxicity (Finley, 1999; Erikson et al., 2002a; Kim et al., 2005). It is also well documented that individuals with chronic liver disease (Hauser et al., 1996; Rose et al., 1999; Montes et al., 2001; Racette et al., 2005), or those receiving parenteral nutrition (Fitzgerald et al., 1999; Bertinet et al., 2000; Takagi et al., 2001), also accumulate high brain Mn levels.

Following chronic exposure to high levels of Mn, patients may present with early psychiatric symptoms, such as increased anxiety, insomnia and irritability (Calne et al., 1994; Pal et al., 1999). Later, as the disorder progresses, they demonstrate movement abnormalities, including dystonia and difficulty in walking backwards (Calne et al., 1994; Pal et al., 1999). Although somewhat similar in presentation to idiopathic Parkinson's disease (IPD), it can be distinguished by the general lack of responsiveness to dihydroxyphenylalanaine (L-DOPA), a highly effective drug used to treat IPD, and the rarity of tremor.

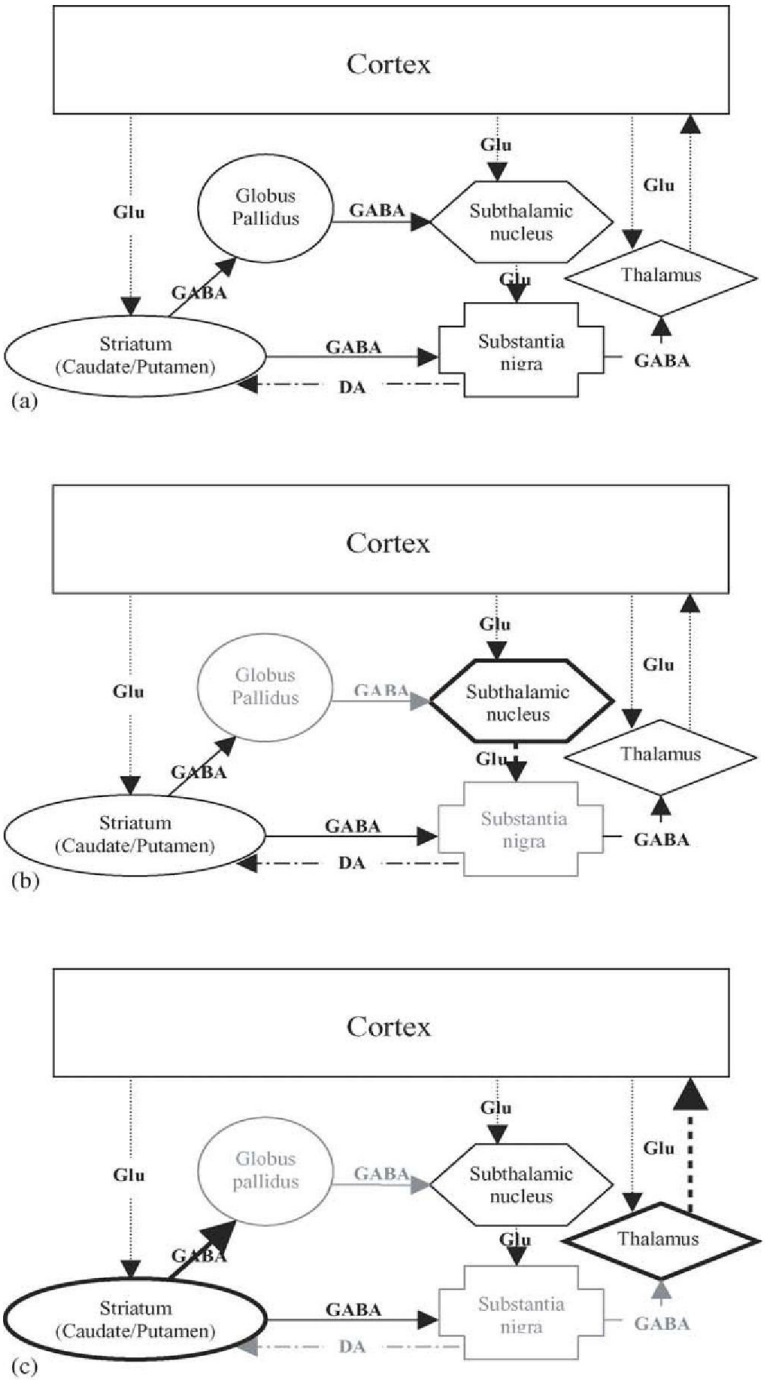

Fig. 1. Schematic of the basal ganglia circuitry and relevant neurotransmitters during (a) non-pathogenic conditions, (b) high Mn or (c) idiopathic Parkinson's disease. Gray nuclei in (b) and (c) are those putatively affected during the respective pathogenic condition, resulting in degeneration and down-regulation of their respective neurotransmitter. Those nuclei with heavy black outlines would be subsequently up-regulated due to the dysinhibition of GABAergic input. Abbreviations: Glu, glutamate; DA, dopamine; GABA, γ-aminobutyric acid.

1.1. The basal ganglia circuitry

It is perhaps not surprising that IPD and manganism share similarities in their clinical presentations. Both diseases affect the basal ganglia, and both include perturbations of the dopaminergic system. However, their pathological etiologies are quite different. For example, IPD results from the loss of the pigmented dopaminergic neurons in the substantia nigra pars compacta (Obeso et al., 2002). On the other hand, Mn initially accumulates in the globus pallidus, a nucleus with y-aminobutyric acid (GABA) projections (Calne et

al., 1994; Pal et al., 1999). Additionally, it has been hypothesized that at least some of the cell death observed in animals given high doses of Mn may be due to excitotoxic lesions from high extracellular levels of glutamate (Glu) (Hazell, 2002; Normandin and Hazell, 2002; Takeda, 2003). It is likely that the characteristics of manganism are due to the interactions of all three of these basal ganglial neurotransmitters.

The nuclei comprising the basal ganglia are responsible for integrating and coordinating information from various brain regions associated with motor movement. As diagrammed in Fig. 1a, the circuitry of basal ganglia is comprised of the following discrete nuclei: globus pallidus, substantia nigra, subthalamic nucleus and the striatum (caudate and putamen). However, the circuit also sends and receives information from the cortex and thalamus. When viewed from the standpoint of a circuit, rather than individual nuclei, it becomes more apparent why IPD and manganism share a common phenotype, as both the globus pallidus and substantia nigra can ultimately be affected in both entities.

With this framework in mind, it is reasonable to hypothesize that an initial insult to the globus pallidus during Mn neurotoxicity could result in decreased inhibitory GABA input to the subthalamic nucleus. This would potentially lead to dysinhibition of the down-stream Glu output to the substantia nigra (Fig. 1b), leading to chronic over-stimulation. A similar scenario can be described for IPD. Here, the initial site of damage is the substantia nigra (Fig. 1c), resulting in a two-fold problem: firstly, decreased dopamine (DA) output to the striatum would indirectly result in deregulation of the globus pallidus; secondly, dysinhibition of the thalamus could lead to increased Glu output to the neurons in the thalamo-cortical pathway. The overall result of injury to the substantia nigra during IPD thus affects the globus pallidus, while damage to the globus pallidus from Mn accumulation subsequently affects the substantia nigra.

Although not thought to be directly related to IPD or Mn neurotoxicity, the glutamatergic system of the basal ganglia is also disrupted in both disorders, due to the involvement of either the thalamus or the subthalamic nucleus, respectively. Glu deregulation can lead to significant cellular consequences, as excess extracellular Glu and its ensuing excitotoxicity are well documented (Danbolt, 2001). 1.2. Neurotransmitters of the basal ganglia GABA is the main inhibitory neurotransmitter in the brain. Its production is intimately related to the regulation of Glu through the astrocytes (Fig. 2). Indeed, it is astrocytes that remove Glu from the synaptic cleft following neurotransmission (Aschner et al., 1999; Aschner, 2000; Normandin and Hazell, 2002). Glu is then converted to glutamine (Gln) and released from astrocytes for uptake by neurons. Finally, Gln is converted back to Glu in glutamatergic neurons, or to GABA in GABAergic neurons. It is also known that GABA dysfunction is associated with various psychiatric disorders, such as schizophrenia, bipolar disorder and major depression (Torrey et al., 2005), which share symptomology with the early stages of manganism.

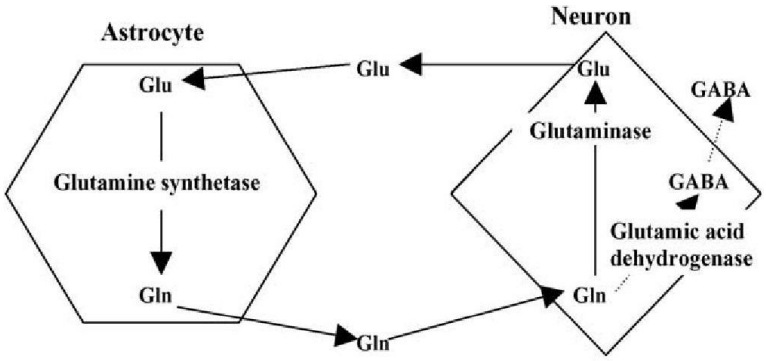

Fig. 2. Interrelationship between glutamate, γ-aminobutyric acid and glutamine. Astrocytes remove the extracellular Glu from the synapse and convert it to the non-excitotoxic amino acid Gln. Gln is subsequently taken up by neurons where it is metabolized to either Glu, in glutamatergic neurons, or GABA, in GABAergic neurons. Abbreviations: Glu, glutamate; GABA, γ-aminobutyric acid; Gln, glutamine.

DA is an important catecholamine in the brain associated with the regulation of locomotor activity, emotion and neuroendocrine secretion (Cooper et al., 1996b). The synthesis of DA is unrelated to that of Glu or GABA (Fig. 3). Dopaminergic, as well as other catecholaminergic neurons, use the amino acid tyrosine as the initial starting material for neurotransmitter synthesis. Following two metabolic steps, DA is available for neural transmission. Glu is the most abundant excitatory neurotransmitter in the brain. It has been proposed that Glu plays several major roles in normal brain function such as cognition, learning and memory as well as development of the central nervous system, including synapse induction and elimination, cell migration, differentiation and death (Cooper et al., 1996a). Furthermore, Glu also plays a signaling role in peripheral organs and tissues, as well as in endocrine cells (Danbolt, 2001). As mentioned above, its synthesis is intimately related to that of GABA (see Fig. 2).

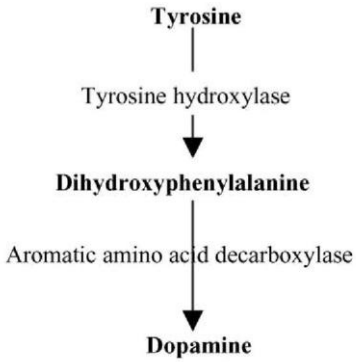

Fig. 3. The synthesis of dopamine from tyrosine. Starting and end products are depicted in bold, while the enzymes responsible for the specific synthetic step are in regular type.

Recently there has been increased interest in determining the exact mechanisms through which Mn exerts its neurotoxicity. Some studies imply that Mn exposure results in increased neuronal oxidative stress (Desole et al., 1997; Stokes et al., 2000). Others propose that brain Mn accumulation disturbs the normal cellular metabolism and uptake of neurotransmitters (Miele et al., 2000; Montes et al., 2003; Fitsanakis and Aschner, 2005). As GABA, Glu and DA are all important neurochemicals in the basal ganglia circuitry, and are likely involved in manganism, it is important to examine the evidence concerning the ability of Mn to disrupt these vital neurochemicals.

2. Mn neurotoxicity and GABA

Although it has been known for many years that the early site of Mn accumulation is the globus pallidus, most research related to Mn neurotoxicity has focused on the dopaminergic system. The probably relates to the clinical similarities of manganism to IPD. Early studies using Mn as a substitute ion for calcium (Ca^{2+}) reported that Mn inhibited the Ca^{2+}- dependent release of GABA (Cotman et al., 1978). Others demonstrated that GABA transport was inhibited by MnCl2 in rat forebrain synaptosomes (Wong et al., 198 1), providing a link between Mn exposure and perturbations in GABA regulation.

One of the first reports specifically examining the effect of Mn on the GABAergic system appeared in 1978 (Bonilla, 1978), where Mn intoxication resulted in increased brain GABA content. Data generated from mice also demonstrated increased GABA levels in the striatum following exposure to either $MnCl_2$ or MMT (Gianutsos and Murray, 1982). The authors do point out, however, that the observed changes in neurotransmitter levels occurred after treatment for either 6 months (MnC_{l2}) or 3 weeks (MMT), but not with shorter exposure paradigms (1–2 months for $MnCl_2$ and several days for MMT). It is perhaps not too surprising that neurotransmitter levels were unchanged following the shorter exposure of $MnCl_2$, since the Mn food content (40 mg Mn/kg feed) was relatively low, and much of the metal would have been cleared by the liver. These data suggest increased striatal stimulation, perhaps from the glutamatergic cortical projections to the striatum (Fig. 1b).

In contrast to these early reports Seth et al. (198 1) found that intraperitoneal injections of 6 mg Mn/kg for 15 days resulted in diminished cerebellar GABA levels (Seth et al., 1981; Lipe et al., 1999). Another group confirmed these data, and also reported decreases in overall brain Glu decarboxylase (GAD) and GABA-transaminase (GABA-T) levels subsequent to intraperitoneal injections of $MnCl_2$ (10–20 mg Mn/kg) daily for 30 days (Chandra et al., 1982). The authors point out that this data is in contrast to that of Bonilla (1978), but suggest that the close relationship of dopaminergic and GABAergic nuclei may reciprocally affect the other's regulation. Chandra et al. (1982) subsequently verified the initial observations in animals on a low protein diet (Ali et al., 1983), or in developing, but not neonatal, rats (Seth and Chandra, 1984). The conflicting results could be due to differences in doses and treatment time. As the globus pallidus is the initial site of Mn accumulation, it may be that GABA output is primarily affected under these treatment conditions.

Interestingly, Ali et al. (1983) report that Mn-induced decreases in brain GABA levels renders rats more susceptible to seizure activity. A similar phenomenon was reported in mice following exposure to MMT (Fishman et al., 1987). However, the latter group attributed the alterations in seizure activity to the potential ability of MMT to inhibit GABAA receptor ligand binding (Fishman et al., 1987). This hypothesis is consistent with work in non-human primates where GABAA receptor density was unchanged (suggesting problems with receptor binding and not receptor levels) following a 26-month dosing regime using 40 mg Mn/kg body mass (Eriksson et al., 1992). It must be noted, however, that both the dose and timeframe involved are higher and longer, respectively, than in earlier studies.

Cell culture data suggest that striatal GABAergic neurons may be more susceptible to Mn exposure than mesencephalic dopaminergic neurons (Defazio et al., 1996). This supports the conclusions of Gwiazda et al. (2002) that low levels of Mn (three injections of 4.8 mg Mn/kg for 5 weeks) increased striatal GABA concentration, but not DA, even in rats pretreated with the dopaminergic neurotoxicant 6-hydroxydo-pamine (6-OHDA) (Gwiazda et al., 2002). Whether DA or GABA levels are affected, however, appears to be strongly dependent on the treatment regime. For example, one lab reported perturbations in both systems (Tomas-Camardiel et al., 2002). This group, however, used aged (18-month-old) rats, which may be a confounder when determining the role of DA in Mn toxicity in younger animals.

Finally, Takeda et al. (2002, 2003) suggested that Mn injected into the striatum could be subsequently released in a sodium-dependent manner through striatal glutamatergic terminals. This release corresponded with a significant striatal GABA decrease in the microdialysate perfusate. Interestingly, no change was observed in striatal Glu, aspartate or glycine levels (Takeda et al., 2003). Notably, this suggests a mechanism whereby GABA release from the medium spiny neurons in the striatum may be regulated via alterations in the neighboring glutamatergic nuclei (Fig. 1b).

Conflicting data exists as to whether Mn accumulation leads to decreases or increases in regional GABA levels. Nevertheless, it is clear that the GABAergic systems in the basal ganglia are affected. Future studies should determine whether GABA nuclei are directly affected by Mn accumulation, or if GABA perturbations are secondary to alterations in neighboring nuclei. Furthermore, the possibility that chronic low doses of Mn may specifically disrupt one neurotransmitter system (GABA), while acute exposures may affect others (DA) should also be tested.

3. Mn neurotoxicity and glutamate

Mn may exert its neurotoxic effects by facilitating the release of excessive amounts of Glu into the extracellular space. Increased extracellular Glu levels may lead to classical NMDA activation and downstream degenerative processes (Danbolt, 2001). Glu levels in the synapse are optimally controlled with 80% of the Glu being removed by astrocytes, a process predominantly carried out by the glutamate:aspartate trans-porter (GLAST). Mn exposure decreases astrocytic Glu uptake (Normandin and Hazell, 2002), as well as GLAST expression is these cells (Erikson et al., 2002b; Erikson and Aschner, 2003), suggesting a potential mechanism by which extracellular Glu levels could be increased.

Mn exposure may also promote excitotoxicity through activation of Glu receptors (GluRs). Spadoni et al. (2000) observed an increase in the sensitivity of postsynaptic receptors to Glu, leading to abnormal activation of pallidal neurons treated with Mn (refer to Fig. 1b). This may partially explain the results of Takeda et al. (2002, 2003) mentioned in the previous section. In contrast, others (Centonze et al., 2001) suggest that chronic Mn treatment leads to increases in the frequency and amplitude of spontaneous excitatory postsynaptic potentials (EPSPs) in the striatum, resulting from hyperactivity of corticostriatal neurons (Fig. 1b). Accordingly, up-stream hyperactivity of cortical neurons, rather than postsynaptic sensitivity to Glu, likely contributes to the Mn intoxication observed in these neurons.

In addition, Mn may affect the glutamatergic system via the over-activation of ionotropic GluRs. Hyperactivity of GluRs may lead to increased energy consumption due to an influx of sodium (Na^+) and Ca^{2+} ions that must be actively pumped out of the cell (Castilho et al., 1999; Gavin et al., 1999; Slemmer et al., 2005). When cells are energy-compromised, it is known that Glu can 'leak' out of cells, resulting in increased extracellular Glu concentrations (Gavin et al., 1999; Erikson and Aschner, 2003; Slemmer et al., 2005). This suggests that Mn may exert its toxic effect by energy deprivation and mitochondrial arrest.

Interestingly, Mn is concentrated in the mitochondria, leading to direct mitochondrial inhibition and decreased ATP levels (Gavin et al., 1999; Danbolt, 2001; Hazell, 2002; Normandin and Hazell, 2002). This process can lead to excessive mitochondrial Ca^{2+} uptake to compensate for decreased Ca^{2+} levels. However, this compensation inhibits the cytoplasmic Ca^{2+} extrusion, a mechanism requiring ATP. The irreversible rise in Ca^{2+} can initiate cell death (Castilho et al., 1999; Gavin et al., 1999). Additionally, Mn exposure alters cellular metabolism. Zwingmann et al. (2003, 2004) demonstrated both an increase in lactate synthesis and glycolytic flux from glucose oxidative metabolism in rats following Mn exposure (50 mg Mn/kg intraperitoneally/day for 4 days). Mn also disrupts astrocyte metabolism (Zwingmann et al., 2003), potentially leading to the inability of astrocytes to provide neurons with the necessary components for neuro-transmitter metabolism (see Fig. 2). It is therefore likely that during Mn poisoning, cells could experience both Ca^{2+} loading within the cytoplasm concomitant with energy deprivation, producing a cytotoxic environment in which the cells can no longer survive.

Finally, Cano et al. (1996) have shown that increases in extracellular Glu can lead to a decrease in glycine binding on the N-methyl-D-aspartate (NMDA) subtype of GluRs. This decline in glycine binding suggests that during Mn poisoning, an increase in Glu is offset by the attenuation of glycine binding, decreasing the affinity of NMDA receptors for Glu. Interestingly, the inability of glycine to bind to the receptor would counter other excitotoxic effects of excessive brain Mn levels.

Due to the diversity of possibilities and contradictions concerning the mechanisms through which Mn perturbs the glutamatergic system, more studies need to focus on clarifying the exact nature of the interactions between Mn accumulation and Glu-induced excitotoxicity. Our current knowledge concerning Mn intoxication, as it relates to Glu, indicates that the presence of Mn: (1) reduces the ability of astrocytes to clear Glu from the extracellular space; (2) increases in the sensitivity of GluRs to Glu; (3) leads to inhibition of mitochondrial activity, causing increased production of reactive oxygen species as well as energy deprivation.

4. Mn neurotoxicity and dopamine

Research on the neurobiological consequences of Mn toxicity conducted in the last two decades has been predominantly directed at the effects of Mn on DA metabolism and its associated behavioral alterations. To date, it remains unknown how and why Mn accumulates in DA-rich brain regions in the basal ganglia, but this increased Mn is inversely related to DA levels both in neonatal (Tran et al., 2002) and older rats (Seth and Chandra, 1984). In this section, we highlight what is known about Mn neurotoxicity and DA biology, focusing mainly on the DA receptor and transporter proteins.

The regulatory action of DA is mediated by at least five receptors classified into two subtypes: D_1-like (D_1 and D_5) and D_2-like (D_2, D_3 and D_4) receptors (Neve and Neve, 1997; Vallone et al., 2000). The D_1-like receptors

are characterized by a long intracellular carboxy terminal, a short external amino terminal, and a short third intracellular loop, that is critical for proper functioning (Sibley et al., 1993; Neve and Neve, 1997). The D_2-like receptors differ in that they have a short carboxy terminal, long amino terminal and a long third intracytoplasmic loop (Sibley et al., 1993; Neve and Neve, 1997). The D_1-like receptors interact with G-proteins that stimulate adenylate cyclase activity, whereas D_2-like receptors inhibit adenylate cyclase activity (Vallone et al., 2000).

Most studies that have examined the effects of Mn neurotoxicity and DA receptors have focused on the D_2 receptor (Seth and Chandra, 1984; Bhargava, 1987; Eriksson et al., 1992). In general, however, they have been inconclusive. For example, Eriksson et al. (1992) reported that Mn intoxication does not significantly alter D_2 receptor levels, but rather D_1 levels in the striatum of monkeys. Others report that striatal D_2 receptor levels are significantly decreased due to Mn toxicity in the developing rat (Seth and Chandra, 1984). Interestingly, many of the behavioral alterations observed in subjects exposed to Mn are DA-related ones, particularly those implicating the D_2 receptor. For example, locomotor and physical activity, both putative dopaminergic-type behaviors, are often impaired in Mn intoxicated rodents (Calabresi et al., 2001; Tran et al., 2002).

Approximately 80% of extracellular DA is recycled into presynaptic neurons through a reuptake Na^+ co-transporter, a 70 kDa protein that is both phosphorylated and glycosylated (Ciliax et al., 1995; Miller et al., 1997). The DA transporter (DAT) is a member of the family of Na^+/Cl--dependent transporters whose regulation includes both chronic and acute regulatory factors (reviewed in Mash and Staley, 1997). DAT density is greatest in caudate, putamen and nucleus accumbens, and increases throughout development to maximal levels in adulthood (Tarazi et al., 1998). Neurotoxicants, such as 1- methyl-4-phenylpyridium (MPP+) and paraquat (pesticide) are selectively lethal to dopaminergic neurons because they are transported by DAT (Snyder and D'Amato, 1986; Ritz et al., 1987). It has been hypothesized that Mn is also transported into dopaminergic neurons via DAT (Ingersoll et al., 1999).

In order to test this hypothesis, Ingersoll et al. (1999) administered cocaine (a DAT inhibitor) or reserpine (effectively results in decreased DA concentrations) to rats exposed to intrathecal Mn (250 μg Mn/rat). Rats exposed to both drugs had a significant decrease in Mn accumulation in the ventral pallidum, suggesting that DAT and/or DA metabolism play a role in mediating Mn neurotoxicity. However, cocaine also affects other neurotransmitters, most notably serotonin and norepinephrine (Ritz et al., 1990). Thus, it is unclear as to whether a decrease in ventral pallidum Mn concentrations is directly related to the inhibition of DAT by this drug, or reflects the inhibition of serotonin and/or norepinephrine transporter functioning.

Using DAT-knockout mice, we recently demonstrated that DAT is involved in the facilitation of striatal Mn accumulation, perhaps playing a critical role in Mn neurotoxicity mediation (Erikson et al., 2005). Specifically, when either wild-type or DAT-knockout mice were exposed to an acutely toxic dose of Mn (50 mg Mn/kg body mass), analysis of regional brain Mn concentrations indicated that DAT-knockout mice accumulated significantly less striatal Mn when compared to wild-type mice. Furthermore, this effect was only evident in the DAT-rich striatum and not other brain regions examined (Erikson et al., 2005). It should be noted that mice lacking DAT (DAT-knockout) have normal anatomical arrangements of dopaminergic cell bodies and projections (Jaber et al., 1999). Therefore, differences in cellular structure should not affect the differential uptake of Mn between DAT-knockout and wild-type mice.

As previously mentioned, manganism shares neurological symptoms with IPD. While IPD is associated with decreased DAT density in the striatum, little is known about the effects of manganism on DAT density and/or functioning. Huang et al. (2003) examined striatal DAT density in Mn intoxicated patients. They found that, compared to controls, there was a slight decrease in DAT density, albeit statistically non-significant in this patient population (Huang et al., 2003). More importantly, these investigators showed that compared to patients with IPD, those with manganism have significantly more DAT in the striatum (Huang et al., 2003). This is corroborated by positron emission tomography (PET) studies with fluora-DOPA imaging in which patients with

manganism show intact dopaminergic neurons, as opposed to those in patients with IPD who display diminished dopaminergic neuronal content (Calne et al., 1994; Pal et al., 1999).

Taken together, these data strongly suggest that Mn neurotoxicity may be in part modulated by DAT. However, this needs to be confirmed by additional studies. It is also likely that one way in which Mn alters DA levels relates to its differential regulation of DA receptors. It could also be the case that alterations in DA receptors occur as a secondary response to potentially increased Glu activity from the subthalamic nucleus, although this has not been demonstrated. Thus, it is important to determine whether changes in receptor numbers are a primary or secondary effect of striatal Mn accumulation.

5. Conclusions

The literature strongly favors the view that high brain Mn levels affect all three of the major neurotransmitters in the basal ganglia circuitry. However, it is still uncertain as to what mechanisms are responsible for the effects of Mn in the brain. Although Mn accumulation occurs initially in the GABAergic globus pallidus, it seems likely that Mn also perturbs the glutamatergic neurotransmission in the cortex and striatum. Additionally, data suggest that, while DA is involved in acute Mn toxicity or the latter stages of manganism, it is plausible that GABAergic nuclei are actually more sensitive to this metal.

Future experiments should focus on which of the basal ganglia nuclei are most susceptible to Mn, along a temporal exposure axis. Because of the propensity of Mn to accumulate in mitochondria (Gavin et al., 1999), it is likely that those basal ganglia nuclei with the highest energy requirements are the most vulnerable, but this has yet to be established. It is also important to determine the effects of pallidal GABA perturbation on other nuclei in the basal ganglia, and better explore the role of GABA and Mn-induced neurotoxicity.

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